2.B. ***Do products that are solely antigingivitis agents, i.e., products that do not significantly reduce plaque, constitute appropriate OTC drug products?***

The Subcommittee concluded that gingivitis is an OTC indication, as indicated in their report to the Agency:

> *"In the early stages of gingivitis when there is little or no pseudopocket formation, only noncalcified plaque, and little or no calculus, thorough daily oral hygiene may resolve the disease. Under these conditions, self-treatment of gingivitis is appropriate. When OTC drug products for the prevention and control of plaque-associated gingivitis are used as part of a program of good oral hygiene, including regular dental checkups, they can help consumers maintain their gingival health."*[15]

The Subcommittee also concluded that

> ***"reductions in plaque mass are inadequate to conclude that a therapeutic effect on gingivitis could be expected."***[16] (emphasis added)

Since the Subcommittee recommended that gingivitis is an OTC indication, and they did not quantitatively relate plaque mass reduction to therapeutic effects on gingivitis, it is reasonable to conclude that those active ingredients that are effective antigingivitis agents, but do not similarly reduce plaque mass, are appropriate OTC active ingredients. There is precedent in other OTC monographs where the active

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[15] Federal Register. 68(103), May 29, 2003, at page 32237.

[16] Ibid.

ingredients have different mechanisms of action; e.g. in the OTC Antitussive Final Monograph, where cough suppression is achieved by a variety of mechanisms[17].

Agents that reduce gingivitis but do not demonstrate a clinically measurable plaque mass reduction can be categorized into two groups: the first group consists of those agents that achieve their gingivitis reduction through a plaque mediated mechanism such as reduction in the plaque virulence (e.g., metabolic factors of specific bacterial pathogens) but may not provide a measurable reduction in overall plaque mass. Other agents may reduce plaque metabolism, providing a "bacterial-static effect" as opposed to a plaque mass reduction. In either case, the pharmacology associated with the gingivitis reduction will be essentially identical to those agents that achieve their gingivitis effect via total plaque mass reduction. Net, as described in the preceding section, agents that achieve gingivitis reduction via a plaque mediated mechanism, other than plaque mass reduction, should clearly be considered as OTC antigingivitis agents and labeling should be provided commensurate with their antiplaque effects.

The second group consists of those agents that may achieve a gingivitis benefit via a non-plaque related mechanism. Agents such as anti-inflammatory agents or imuno-modulators act directly on the host response to the bacterial challenge. It is not clear, based on the long safe use of chronic anti-inflammatory agents that these agents will have a deleterious masking effect of more serious periodontal disease. We would argue that potential benefits of these agents likely outweigh the potential negatives so that individual safety profiles of these ingredients should dictate OTCness. Rather that trying to come to a general conclusion in the absence of data, we recommend that the FDA consider these types of agents on a case-by-case, weight of the evidence basis.

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[17] Federal Register. 41(176) September 9, 1976date, p. 38338.

It is important to reiterate that all Category I active ingredients listed in the OTC Antigingivitis/Antiplaque ANPR have measurable antiplaque effects in some form or another (reduction of plaque mass, plaque virulence or bacterial composition) and none have demonstrated clinically significant anti-inflammatory properties to our knowledge. Hence, any concerns as to an 'undefined' mechanism of antigingivitis efficacy for these Category I agents would appear to be unfounded. On the other hand, we would suggest that in the future, antigingivitis agents that prevent, control or reduce gingivitis by a non-plaque related mechanism should also be considered as viable OTC drugs as long as safety and effectiveness of the antigingivitis active ingredient are established. This type of active ingredient would not carry antiplaque labeling but should be permitted to make other truthful and nonmisleading claims that accurately describe the pharmacologic action of the drug and its intended use.

The Agency's concern in the preamble to the ANPR regarding antigingivitis active ingredients with non-plaque mechanisms of action appears to be that there is a potential for masking symptoms of a more serious disease, e.g. periodontitis. As stated previously, we believe there are several antiplaque mechanisms which impact the pathogenicity of plaque to disrupt its contribution in the cascade of events which contribute to the development of gingivitis and periodontal disease in general and that all the recommended Category I actives (CPC, SnF_2 and essential oils) possess at least one of these mechanisms. The benefit of having a safe and effective antigingivitis active ingredient in the marketplace that does not similarly reduce the accumulation of plaque mass in certain clinical settings does not carry any proven risk for the development of periodontitis. It should be recognized that stannous fluoride, the unique ingredient discussed herein, has been marketed for anticaries effects for over 50 years without demonstrating any concerns for masking periodontal disease. Most importantly, there is no doubt that appropriate labeling and professional education can be developed for all antigingivitis active ingredients to ensure that consumers are directed to their dental professional for regular dental check-ups.

Lastly, it must be recognized that chemotherapeutic agents in dentifrice and rinse products or in future NDAs will be used as part of a regimen that includes brushing, flossing and regular dental visits which should help alleviate concerns of masking disease. Directions and other usage information on package labeling directing consumers to traditional oral hygiene practices (brushing, flossing) and regular dental visits are known to assist in the control of gingivitis and periodontal disease.